TOYA129.008APC PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Shirai, et al.

App. No : 10/521,958

Filed: January 21, 2005

For : INDOMETHACIN EXTERNAL

PREPARATION

Examiner : Jean-Louis, Samira

Art Unit : 1617

Conf No. : 2101

 $2^{\rm nd}$ DECLARATION OF MAKOTO KANEBAKO AND HITOMI CHIBA UNDER 37 C.F.R. \S 1.132

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dear Sir:

We, Makoto Kanebako and Hitomi Chiba, declare as follows

- 1. We are researchers in KOWA Company Fuji Research Laboratory. We are familiar with the Office Actions, cited references and claims of the above-referenced application.
- 2. In order to establish the criticality of a melting point temperature of 40°C or higher, the following experiments were performed. Gel-cream formulations were prepared as described in U.S. Application No. 10/521,958 for Example Formulations 1-3 and Reference Formulations 1-8. See Table 1 (attached).
- 3. Example Components Glyceryl monostearate, Sorbitan monostearate and Stearyl alcohol having a melting point of 40°C or higher were compared to analogs having a melting point of less than 40°C. The Example and Reference Components are shown in Table 2 (attached).

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4. Example 1 and References 1 and 2 relate to glycerin fatty acid ester. As shown in Table 2, Glyceryl monostearate has a melting point higher than 40°C, but Reference Components 1 and 2, Glyceryl undecylenate and Glyceryl isostearate have melting points under 40°C. In the case of Glyceryl undecylenate, the melting point is 36°C, just under 40°C. Referring to Table 1, there is no phase separation for Glyceryl monostearate even at one month, whereas phase separation in the two Reference Components is observed at 2 weeks. We conclude that within the genera of glyceryl fatty acid esters, only species having a melting point of 40°C or higher (such as Glyceryl monostearate) can be stored without phase separation in a gel-cream formulation.

- 5. Example 2 and References 3, 4, and 5 relate to Sorbitan fatty acid ester. As shown in Table 2, Sorbitan monostearate has a melting point of 40°C or higher. Sorbitan monostearate was compared to three analogs. Sorbitan monoisostearate and Sorbitan monooleate both have the same number of carbon atoms as Sorbitan monostearate (18) but lower melting points. Sorbitan monolaurate has 12 carbons. As shown by the Data of Table 1, there is no phase separation for Sorbitan monostearate having a melting point of 40°C or higher at one month storage. In contrast, Reference Components 3 and 5 showed phase separation at 2 weeks and Reference Component 4 showed phase separation at one month. We conclude that gel-cream formulations which include Sorbitan fatty acid esters with a melting point of 40°C or higher can be stored without phase separation while analogs having a melting point below 40°C cannot be stored without phase separation.
- 6. Example 3 and References 6, 7, and 8 relate to fatty alcohol. As shown in Table 2, Stearyl alcohol has a melting point of 40°C or higher. The Reference Components, Octyl alcohol, Decyl alcohol and Lauryl alcohol, all have melting points below 40°C. As shown in Table 1, gelcreams formulated with Stearyl alcohol do not show phase separation at one month while the formulations using the fatty alcohols having lower melting points were not even stable initially. We conclude that fatty alcohols having a melting point of 40°C or higher are effective in gelcream formulations to prevent separation upon storage whereas fatty alcohols having a melting point below 40°C are not effective.

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7. The stabilizing effect of surfactants having a melting point of 40°C or higher in gel-cream formulations and the criticality of the higher melting point could not have been predicted based upon the disclosures of Kimura (JP 10-182458) and Inagi (US 4309414).

We declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States codes and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: <u>November</u> 18, 2008

Dated: <u>November</u> 14, 2008

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Result of the Experiment

Table 1

					Fo	Formulation	uc				
Component	Example 1	e Example 2	Example 3	Reference 1	Reference 2	Reference 3	Reference 4	Reference 5	Reference 6	Reference Reference	Reference 8
Indomethacin	7	1		۲.	-1	1	ŗi	-4	r.	ı,	-
Octvldodecyl Myristate	S	5	5	2	5	5	ស	r,	ಬ	5	5
Diisopropyl Adipate	2	S	S	ಬ	ß	ഹ	သ	ഗ	ស	ഗ	ស
Carboxyvinyl polymer	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1-Methylcellulose	2910 0.5	0.5	0.5	0.5	0.5	0.5	6.5	0.5	0.5	0.5	0.5
L-menthol.	m	3	3	3	3	3	3	3	3	8	3
Polvethylene glycol 400	Ľ.	-	e=i	1	1	ï	1	1	Ţ	ī	1
Isopropanol	36	36	36	36	36	36	36	36	36	36	36
ED'na-2na	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Sodium bisulfite	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Di Sopropanolamine	0.8	0.8	0.8	8.0	0.8	0.8	8.0	8.0	0.8	8.0	8.0
Water	44.2	45.7	44.2	44.2	44.2	45.7	45.7	45.7	44.2	44.2	44.2
Glyceryl monostearate (C18)	2	1	ı	ı	1	ı	1	.1	1	ı	1
Sorbitan monostearate (C18)	ı	0.5	I	_		1	1	-	i.	1	ı
Stearyl alcohol (C18)	1	ı	\$		ł	ī	1	1	E	-	t
Glyceryl undecylenate (C10)	1	1	1	2		I		-	***	J	1
Glyceryl isostearate (C18)	1	į.	1	1	7	ı	i	1	-	ı	1
1	ı	1	ł		t	0.5	_	_	t	_	1
Sorbitan monoisostearate (C18)	ı	l	1	1	-	ı	0.5	1	•	1	1
Sorbitan monooleate (C18)	1	-	ı	1	1	ſ	ſ	0.5	ı	-	-
Octyl alcohol (C8)	1	1		ı	ı	1	1	1	2	1	
Decyl alcohol (C10)	ų	(1	ı	ı	1	ſ	ı	ŧ	2	j
Lauryl alcohol (C12)	ı	j	1	ι	1	ı	ł		ſ	ı	2
Melting point of surfactant (°C)	54-58	8 55-59	56-58	36	below25	13-14	below25	-10	-1.5	7	24-27
Initial	0	0	0	0	0	0	0	0	×	×	×
separation Stored for 2 week (5°C)	(3,5)	0	0	×	×	×	0	×	×	×	×
Stablinty Stored for 1 month (5°C)	(2,5)	0	0	×	×	×	×	×	×	×	×
Criteria for evaluation	<o; <x;="" phase="" phase<="" td=""><td></td><td>separation wa separation wa</td><td>was not obserwas observed></td><td>observed> :rved></td><td></td><td></td><td></td><td></td><td></td><td></td></o;>		separation wa separation wa	was not obserwas observed>	observed> :rved>						

Table 2 Deta

ומחדם כ	Decall descri	Decail description of surfactant		
	Component	Commercial product	Melting point	Length of carbon chain
Example 1	Glyceryl monostearate	NIKKOL MGS-F20	54~58°C	C18
Reference 1	Glyceryl undecylenate	NIKKOL MGU	36°C	C10, unsaturated fatty acid
Reference 2	Reference 2 Glyceryl isostearate	NIKKOL MGIS	below 25°C	C18, branched fatty acto
Example 2	Sorbitan monostearate	NIKKOL SS-10M	55~59°C	C18
Reference 3	Reference 3 Sorbitan monolaurate	RHEODOL SP-L10	13~14°C	010
Reference 4	Sorbitan monoi	sostearate NIKKOL SI-10RV	Delow 25°C	Cla branchod forther
Reference 5	Sorbitan monoo	RHEODOL SP-010V	-10°C	C10 mestinged facty acid
Example 3	Stearyl alcohol	NIKKOL Stearyl alcohol	2°85~95	City unsacutated tarry acid
Reference 6	Reference 6 Octyl alcohol	KALCOL0898	-15°C	0.40
Reference 7	Reference 7 Decyl alcohol		7°C	010
Reference 8	Reference 8 Lauryl alcohol	KALCOL2098	J-60	21.5